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PERSPECTIVES IN RENAL MEDICINE

Renoprotection: One or many therapies?

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Renoprotection: One or many therapies?

Background. Renal disease that progresses to end-stage renal disease (ESRD) imposes a great burden on the affected individual and on society, which mainly bears the cost of ESRD (currently more than $10 billion to treat about 333,000 patients annually in the U.S.). Thus, there is a great need to identify therapies that arrest the progression mechanisms common to all forms of renal disease. Progress is being made. Perhaps the most visible advance is the randomized controlled trials (RCT) demonstrating the renoprotective effects of angiotensin-converting enzyme (ACE) inhibitors. There are also numerous other promising renoprotective therapies. Unfortunately, testing each therapy in RCT is not feasible. Thus the nephrologist has two choices: restrict renoprotective therapy to those shown to be effective in RCT, or expand the use of renoprotective therapies to include those that, although unproven, are plausibly effective and prudent to use. The goal of this work is to provide the documentation needed for the nephrologist to choose between these strategies.

Methods. This work first describes the mechanisms believed to be involved in the progression of renal disease. Based largely on this information, 18 separate interventions that slow the progression are described. Each intervention is assigned a level of recommendation (Level 1 is the highest and Level 3 the lowest) according to the strength of evidence supporting its renoprotective efficacy.

Results. The number of interventions at each level of recommendation are: Level 1, $N = 4$; Level 2, $N = 4$; Level 3, $N = 10$. Our own experience with the multiple-risk-factor intervention is that most patients can achieve the majority of the Level 1 and 2 interventions, and many of the Level 3 interventions. We recommend the expanded renoprotection strategy.

Conclusion. This work advances the hypothesis that, until better information becomes available, a broad-based, multiple-risk-factor intervention intended to slow the progression of renal disease can be justified in those with progressive nephropathies. This work is intended primarily for clinical nephrologists and thus each recommended intervention is described in substantial practical detail.

Key words: angiotensin II, progressive renal disease, ACE inhibitors, multiple-risk-factor intervention, glomerular filtration rate, hypertension.

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The term "renoprotection" often evokes a single image: angiotensin-converting enzyme (ACE) inhibition therapy to slow the "progression of renal disease." ACE inhibitors certainly deserve that reputation [1]. Nevertheless, this therapy alone rarely stops renal disease progression. Herein, we describe a multiple-risk-factor intervention strategy based on inhibiting the progression mechanisms believed to be common to most forms of progressive renal disease. To assist the treating physician, each intervention is described in substantial practical detail and prioritized according to level of recommendation. The incentive to use the multiple-risk-factor intervention is that each intervention is either of proven value or plausibly effective and prudent to use. Furthermore, renal disease generally progresses slowly [glomerular filtration rate (GFR) loss of about 3 mL/min/year] [2]. Thus, even small improvements in slowing renal disease progression can provide large benefits (Fig. 1). Our hypothesis is that the benefit of the multiple-risk-factor intervention is the summation of multiple small beneficial effects.

In the present context, "progression of renal disease" refers to an irreversible decline in GFR because of structural damage to the renal vasculature, tubules or interstitium. In most studies of progression of renal disease, histologic documentation of structural damage was not demonstrated by renal biopsy. Rather, it was assumed because the loss of GFR was irreversible.

The renoprotective strategies proposed are based on clinical and experimental studies that have examined the mechanisms of renal disease progression. The interactions of these mechanisms with each other are probably exceedingly complex. To illustrate this point consider Figure 2. This paradigm explains how blood pressure control might slow the progression of renal disease through its effect to decrease proteinuria. This paradigm would become far more complex if it included the other relevant mechanisms of renal disease progression.

A further reason to eschew a comprehensive paradigm is that we do not have a clear idea of how the various renoprotective mechanisms interact. For example, the optimal use of ACE inhibitors (ACE I) for renoprotection has not been clarified by the randomized trials be-

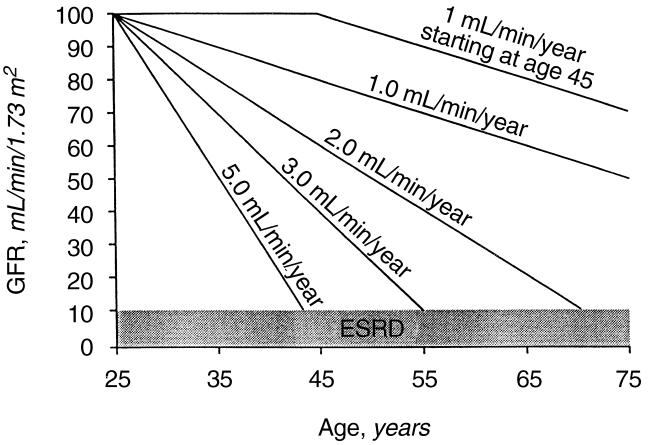

Fig. 1. Rate of glomerular filtration rate (GFR) decline in normals and in hypothetical patients with onset of progressive renal disease at age 25. The course of GFR decline with normal aging (top curve) is based on a cross-sectional study of iothalamate clearance in 357 patients aged 17 to 70 years [7]. Note that a GFR loss of greater than 1 mL/min/year beginning at age 25 can result in end-stage renal disease within a normal lifespan. Note also that small differences in rates of GFR decline can result in large differences in time to onset of end-stage renal disease.

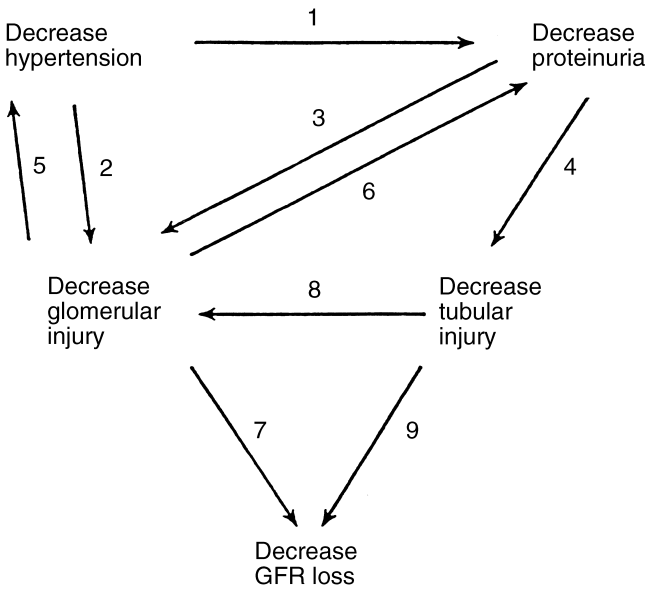

Fig. 2. Possible interactions of hypertension, proteinuria, and glomerular filtration rate (GFR) loss in patients with glomerulopathy. The interactions are shown as numbered arrows. It is proposed that arrows 1 through 4 represent primary effects of the interactions. The relative importance of these primary and secondary effects is unknown (reprinted from Hebert et al, with permission of the International Society of Nephrology) [11].

cause blood pressure control in those trials was not optimal. Specifically, the Modification of Diet in Renal Disease (MDRD) Study (which was published after the ACE I studies were begun) showed that in proteinuric renal disease, systolic blood pressures in the low 120s mm Hg slowed the progression of renal disease better than systolic blood pressures in the low 130s mm Hg [2]. In contrast, in the randomized trials that tested ACE I renoprotection (the MDRD Study used ACE I but not as randomized intervention), the mean achieved systolic blood pressure was typically in the 140s mm Hg [3, 4]. Also, the randomized trials used only low to moderate doses of ACE I [5]. Thus, the optimum renoprotective ACE I dose and blood pressure level have not been clarified by the randomized trials [6].

In light of the uncertainty of how renoprotective mechanisms interact when they are deployed simultaneously, later in this article, we simply list the mechanisms and interventions, both the proven and plausible, and their possible modes of action. Patients with autosomal polycystic kidney disease (ADPKD) merit special considerations with respect to progression mechanisms and therapeutic interventions. These are discussed in relationship to each of the relevant mechanisms or therapies. The mechanisms of renal disease progression are discussed first, followed by the recommended interventions, which are ranked according to the level of recommendation.

MECHANISMS OF RENAL DISEASE PROGRESSION

Hypertension

Increased blood pressure may impair kidney function by inducing arteriolar nephrosclerosis [7]. Glomeruli are generally spared, unless the hypertension is severe. Thus, proteinuria is usually minimal in progressive hypertensive arteriolar nephrosclerosis, a condition rarely seen in Caucasians but often seen in African Americans [8]. Hypertension-induced tissue injury may involve stretch-induced tissue fibrosis [9] and up-regulation of intercellular adhesion molecules, which results in renal infiltration of lymphocytes and macrophages [10]. When hypertension is superimposed on intrinsic renal disease, the resulting arteriolar nephrosclerosis adds to renal disease progression. In proteinuric renal disease, hypertension creates a vicious cycle promoting progression of renal disease (Fig. 1) [11]. This cycle is particularly adverse in African Americans [8].

Proteinuria

Nonselective proteinuria contains numerous toxic/inflammatory systems that promote the progression of renal disease [reviewed in 12, 13]. The best studied toxic/inflammatory systems are complement, inflammatory lipoproteins, iron species, and protein overload of proximal tubular epithelial cells. All components of the alternative complement pathway are present in nonselective proteinuria. Membrane attack complex (MAC; C5b-9) is deposited on proximal tubular epithelium [14] causing tubular and interstitial injury [15, 16]. Inflammatory lipoproteins interact with renal tubular epithelial cells inducing chemokines, which promote inflammation. Filtered

serum iron or transferrin induces free oxygen radical formation, which is toxic to renal tubular epithelial cells. An overload of the protein transport systems of proximal tubular epithelial cells leads to induction of chemokines [17], nitric oxide (NO) [18], and growth factors such as transforming growth factor-β (TGF-β) [19].

These toxic/inflammatory compounds probably induce (*1*) glomerular injury mainly to podocytes promoting proteinuria [20]; (*2*) tubular injury from C5b-9 deposition, inflammatory cell infiltration (induced by chemokines), and free radical formation (induced by Fe^{3+}); and (*3*) tubular epithelial hyperplasia from growth factors and mitogens induced by proteinuria through complement [21, 22] and by filtered insulin-like growth factor-1 (IGF-1) [23]. These are apparently responsible for the proximal tubular epithelial cell hyperplasia that encroaches on tubular lumen in proteinuric renal disease [13]. Finally, these compounds induce tubulointerstitial fibrosis by proteinuria-induced TGF-β and endothelin-1 (ET-1) [reviewed in 17].

Excess angiotensin II

Angiotensin II (Ang II) may promote renal disease progression by inducing glomerular hypertension, glomerular hypertrophy, mitogens such as platelet-derived growth factor (PDGF), fibrosis through TGF-β or ET-1, ammonia formation leading to activation of the alternative complement pathway, inflammatory intracellular signaling mechanisms, including nuclear transcription factor κB (NF-κB), increased tubular absorption of sodium and oxygen consumption, increased oxidant stress, and increased aldosterone leading to increased blood pressure and tissue fibrosis [reviewed in 1, 12, 24]. Ang II also increases expression of monocyte chemoattractant protein-1 (MCP-1), a potent chemokine [25, 26] that can induce inflammation and fibrosis through TGF-β [25]. Ang II increases plasminogen activator inhibitor-1 (PAI-1) favoring thrombosis and progressive sclerosis [27].

Hyperglycemia

Elevated blood glucose causes glomerular hyperfiltration, hypertrophy, and hypertension. High glucose induces renal matrix proteins, which accumulate and interfere with vascular function. These can occur with even mild hyperglycemia if it is of sufficient duration and with appropriate genetic risk factors [28].

Increased protein intake

Protein ingestion acutely increases GFR and proteinuria apparently by increased renin and eicosanoids and effects of individual amino acids [29], including NO production by L-arginine [30]. These effects persist if the increased protein intake is sustained [2]. Thus, glomerular hyperperfusion and increased proteinuria may explain the adverse effects of increased protein intake on renal disease progression.

Increased NaCl intake

In the MDRD Study, baseline urinary sodium excretion (reflecting NaCl intake) was not an independent risk factor for the progression of renal disease [31]. Nevertheless, high salt intake can override the antiproteinuric effect of ACE I and calcium channel blocker therapy [32, 33], and this could promote renal disease progression.

Increased fluid intake

Analysis of the MDRD database showed that higher follow-up mean 24-hour urine volume and lower mean 24-hour urine osmolality during follow-up were associated with more rapid GFR decline, particularly in ADPKD patients (abstract; Hebert et al, *J Am Soc Nephrol* 11:148A, 2000). The high urine volumes were associated with maintained or increased blood pressure and greater diuretic use. Thus, the high urine volumes were not explained by more aggressive renal disease causing a renal concentrating and salt-wasting defect and polyuria. If chronically high urine volume promotes progression of renal disease, the effect may be due to adverse effects of increased intratubular pressure caused by high urine volume.

Hyperlipidemia

Elevated plasma lipids adversely influence the progression of experimental nephropathy [34]. There have been no definitive controlled clinical trials in patients that demonstrate a benefit from lipid control on the progression of renal disease [34]. Hyperlipidemia could adversely affect glomerular function because of the uptake of oxidized lipoproteins [34]. Hyperlipidemia can also lead to atherosclerosis of the renal arteries and its major branches, particularly in the older population (unpublished observations).

Cigarette smoking

Smoking has vasoconstrictor, thrombotic, and direct toxic effects on the vascular endothelium. Cigarette smoking is an independent risk factor for progression of inflammatory renal disease (IgA nephritis), noninflammatory renal disease (ADPKD), and diabetic nephropathy [reviewed in 35].

Increased plasma homocysteine

Hyperhomocystinemia develops as GFR declines (abstract; Falkenhain et al, *J Am Soc Nephrol* 10:163A, 1999) [36] apparently as a result of changes in renal metabolism rather than decreased urinary excretion [36]. Hyperhomocystinemia is a risk factor for atherothrombosis [37] and microalbuminuria in diabetic nephropathy [38], pos-

sibly because of endothelial injury by oxidant stress. A recent study did not find a significant correlation between plasma homocysteine and progression of renal disease [39]. This is not surprising given the small size of the study.

Increased endogenous insulin (increased C-peptide)

Insulin resistance is a cardiovascular risk factor in humans [40]. In experimental models of insulin resistance, high plasma insulin levels (and/or triglycerides) induce glomerular sclerosis [41] perhaps because insulin induces fibrosis and glomerular hyperperfusion [40]. These effects might explain the association of microalbuminuria with insulin resistance in nonobese subjects and the increased incidence of focal and segmental glomerulosclerosis (FSG) in obese individuals and African Americans [42], both of whom often manifest insulin resistance.

Nonsteroidal anti-inflammatory agents

Nonsteroidal anti-inflammatory agents (NSAIDs) cause acute and usually reversible decreases in GFR, and idiosyncratic forms of membranous nephropathy and interstitial nephritis, both associated with nephrotic syndrome [43]. The literature is less clear as to whether chronic daily use of NSAIDs causes progressive nephrotoxicity [43]. However, our clinical experience strongly suggests that it does (unpublished observations).

Hyperphosphatemia

Animal models and human studies indicate that hyperphosphatemia promotes progression of renal disease, perhaps by causing renal calcium and phosphorus deposition and/or hyperparathyroidism [44].

Anemia

A small-randomized trial in patients suggested that if blood pressure is controlled, renal disease progression is slowed by correction of the anemia with erythropoietin [45]. The possible mechanism is unclear; however, glomerular damage impairs renal blood flow and may cause renal hypoxia, which is a fibrogenic stimulus [46].

Excess aldosterone

Mineralocorticoids appear to induce myocardial and renal fibrosis, perhaps through increased expression of plasminogen activator-1 (PAI-1) [24].

Potassium depletion

Sustained potassium depletion can be associated with progressive renal interstitial fibrosis [47]. The mechanism may be induction of growth factors and matrix production factors, including those in the TGF-β family. Potassium depletion in experimental animals also induces renal hypertrophy, apparently through induction of growth factors [48].

Increased levels of procoagulants

Above-average levels of fibrinogen, factor VIII, and von Willebrand factor were independently related to increased serum creatinine during follow-up of the 12,208 patients in the Atherosclerosis Risk in Community (ARIC) Study (abstract; Coresh et al, *J Am Soc Nephrol* 10:606A, 1999).

Gender

Renal diseases usually have a higher prevalence and more rapid progression in men than women [49]. The postulated mechanisms include estrogen's favorable effects on glomerular hemodynamics, blood lipids, cytokines that promote progression via mitogenic growth, and fibrosis [49]. Estrogen therapy raises blood pressure. Nevertheless, women have lower blood pressure than men [49]. Estrogens antagonize the effects of aldosterone, which could lessen the postulated fibrogenic effect of aldosterone [24].

A MULTIPLE-RISK-FACTOR INTERVENTION STRATEGY TO SLOW THE PROGRESSION OF RENAL DISEASE

The strategy for the multiple-risk-factor intervention is based on the proven and the plausible mechanisms of progression of renal disease, as discussed previously in this article. The therapeutic interventions we recommend are listed in Table 1 according to the level of recommendation. Level 1 (highest) recommendations are based on the primary analysis of one or more large clinical trials that are prospective, randomized, and controlled. Level 2 (intermediate) recommendations are based on a secondary analysis of one or more of the trials that provided Level 1 recommendations, high-quality case control studies, or randomized controlled trials that involved relatively small numbers of patients. The Level 3 (lowest) recommendations are based on observational studies or studies in experimental renal disease. Each renoprotective intervention is discussed in more detail in the following paragraphs.

1. Control blood pressure (Level 1)

The belief that blood pressure control is important in slowing progression of renal disease has been strongly held for decades; however, this belief was not confirmed until 1994 when the MDRD Study published its results of its randomized intervention study [2]. The key findings and our recommendations based on those findings are as follows:

In those with proteinuria >1 g/24 hours, the low blood pressure goal (mean achieved blood pressure ~125/75 mm Hg) slowed progression of renal disease better than the usual blood pressure goal (mean achieved blood pressure ~135/85 mm Hg).

The greater the proteinuria, the greater was the benefit

Table 1. Renoprotective strategies ranked according to level of recommendation

Intervention	Goal/comments
1. Control blood pressure (Level 1)	Sitting systolic blood pressure in the 120s or lower, if tolerated. This goal is recommended for all patients with progressive renal disease but it is particularly important if proteinuria >3.0 g/24 hours. Text has recommended antihypertensive regimens.
2. ACE inhibitor therapy (Level 1) Angiotensin receptor blocker (ARB) if ACE inhibitor intolerant (Level 3)	Use ACE I even if normotensive. Renoprotection has been demonstrated with low- to moderate-dose ACE I therapy. Optimum dose is unknown. If proteinuric, goal is to reduce proteinuria to <1.0 g/24 hours. ACE I should be used primarily to achieve the proteinuria goal. ACE I generally are not potent antihypertensive agents in chronic renal insufficiency. Thus escalation of the ACE I dose should not be the primary means to achieve the blood pressure goal.
3. Control blood glucose in diabetics (Level 1)	In type 1 diabetics, goal is hemoglobin A1C (Hgb A1C) within 2 percentage points of the upper limits of normal of the given assay. In type 2 diabetics, goal is normal Hgb A1C.
4. Dietary interventions Protein intake (Level 1)	Goal is 0.7 to 0.8 g/kg ideal body weight/day. To achieve goal, may need to instruct @ 0.6 g/kg ideal body weight/day.
NaCl intake (Level 3)	NaCl 80 to 120 mmol/24 hours (~2.0 to 3.0 g Na intake) to optimize the antiproteinuric effect of ACE I, ARB or CCB therapy. NaCl restriction does not apply if renal salt wasting is present. $NaHCO_3$ therapy does not count towards dietary NaCl goal.
Fluid intake (Level 2)	A high fluid intake that results in a 24-hour urine volume exceeding 2.0 L/24 hours is not beneficial and might be associated with more rapid GFR decline. This recommendation does not apply if nephrogenic or hypothalamic diabetes insipidus is present. ADPKD patients may particularly benefit from avoidance of a high fluid intake.
5. Control blood lipids (Level 1 for cardiovascular benefit, Level 2 for renal benefit)	LDL cholesterol <120 mg/dL (<100 mL/dL may be even better especially if atherosclerosis is present or suspected). HMG CoA reductase inhibitor therapy, which lowers LDL cholesterol may also have anti-inflammatory effects that are renoprotective.
6. No cigarette smoking (Level 1 for general benefit, Level 2 for renal benefit)	No cigarette smoking.
7. Avoid regular use of NSAIDs (Level 3 based on published evidence, Level 1 based on clinical experience)	NSAIDs once or twice weekly (e.g., for headaches) seems safe. See text for discussion of alternatives to NSAIDs.
8. Control plasma homocysteine (Level 2 for cardiovascular benefit, Level 3 for renal benefit)	Use folic acid (2 to 15 mg daily) to reduce total plasma homocysteine to normal. May be difficult in advanced renal insufficiency. Blood vitamin B_{12} levels must be normal. Vitamin B_6 and B_{12} supplement may be necessary.
9. Control hyperinsulinemia (Level 2 for cardiovascular benefit, Level 3 for renal benefit)	Lose excess weight, exercise, hyperinsulinemia (elevated C-peptide) is a strong cardiovascular risk factor and may promote glomerulosclerosis.
10. Use antioxidants (Level 3)	Vitamin C 200 mg daily is recommended. Vitamin E might also be useful.
11. Correct anemia (Level 1 for general benefit, Level 2 for renal benefit)	Hemoglobin 11 to 12 g/dL is recommended. Erythropoietin therapy is usually necessary.
12. Avoid hypokalemia (Level 1 for general benefit, Level 3 for renal benefit)	May be especially important to avoid hypokalemia in ADPKD to prevent cyst growth.
13. Control hyperphosphatemia (Level 1 for general benefit, Level 3 for renal benefit)	The goal is normal serum phosphorus level. Dietary phosphorus restriction and phosphorus binder may be needed.
14. Low dose aspirin therapy (Level 1 for general benefit, Level 3 for renal benefit)	The goal is to attenuate the effects of increased procoagulants to promote progression of renal disease. Aspirin, 81 mg daily, is recommended. Do not use if blood pressure is not controlled or if renal bleeding occurs. Addition of dipyridamole therapy may provide further benefit.
15. Estrogen replacement therapy in women (Level 2 for general benefit, Level 3 for renal benefit)	The goal is the usual level of estrogen replacement in post-menopausal women with renal disease for whom no contraindications for estrogen therapy are present. Estrogen effects may explain the slower progression of renal disease in women compared to men.

See text for definition of level of recommendation and further detail regarding each intervention, as well as for a description of the patients for whom these interventions are recommended. Abbreviations are in the **Appendix**.

of achieving the low blood pressure goal. Those with minor proteinuria (<1 g/24 hours) generally had slow rates of GFR decline (~3 to 4 mL/min/year), and this rate of GFR decline was affected little by the low blood pressure goal over the 2.2 years of follow-up in the MDRD Study. In contrast, those with heavy proteinuria (>3.0 g/24 hours) generally had rapid rates of GFR decline (~7 to 14 mL/min/year). These patients derived great benefit from assignment to the low blood pressure goal whose GFR decline was approximately 7 mL/min/year compared with approximately 13 mL/min/year for those assigned to the usual blood pressure goal. Proteinuric African Americans especially benefited by achieving the low blood pressure goal [8].

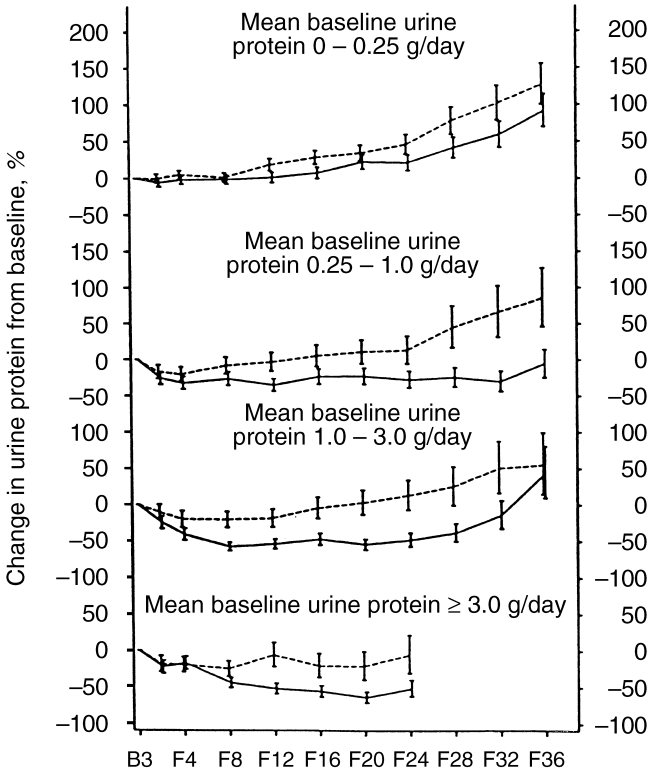

Fig. 3. Changes in urine protein from baseline to selected follow-up times in study A. This is a comparison of changes from baseline in urine protein between patients in the usual (dotted line) and the low (solid line) blood pressure groups within subgroups defined according to baseline proteinuria. Proteinuria was log transformed. Changes in proteinuria are expressed as percentage changes. Three hundred five patients had baseline proteinuria of 0 to 0.25 g/day (mean 0.08 g/day). One hundred twenty had baseline proteinuria of 1.0 to 3.0 g/day (mean 1.8 g/day), and 55 had baseline proteinuria of 3.0 g/d or more (mean, 4.8 g/day; reprinted with permission from Peterson et al, *Annals of Internal Medicine*) [50].

Achieved systolic blood pressure predicted GFR decline better than achieved diastolic blood pressure. For example, in study A (baseline GFR 25 to 55 mL/min/1.73 m^2), the achieved systolic blood pressure adjusted for the 11 relevant covariates of renal disease progression accounted for 9.5% of the variance in GFR decline, while similarly adjusted achieved diastolic blood pressure accounted for only 2% of the variance in GFR decline [50].

The low blood pressure goal did not significantly slow GFR decline in those with proteinuria <1.0 g/24 hours. Nevertheless, it significantly slowed the increase in proteinuria over time that typically occurs in progressive renal disease. This phenomenon is illustrated in Figure 3. Thus, achieving the low blood pressure goal delays the onset of major proteinuria and therefore can be regarded as renoprotective, even in those with minor proteinuria [5].

The low blood pressure goal did not increase cardiovascular or other risks. The low blood pressure goal was well tolerated in the MDRD Study; however, the MDRD Study excluded patients with major cardiovascular diseases. Thus, it is possible that some patients may not tolerate the low blood pressure goal.

The fall in GFR of ADPKD patients in the MDRD study was not slowed by the low blood pressure goal [51]. However, the low blood pressure may slow ADPKD progression if therapy is begun before 50% of GFR is lost [52].

Method for assessing blood pressure control

Blood pressure is taken in the sitting position and after the patient has taken that morning's antihypertensive medication. If the patient's office blood pressure is not at goal, home blood pressure monitoring using calibrated equipment and proper technique is recommended. If home blood pressure is accurately measured, we recommend that it be taken as the extent to which the patient is achieving his/her blood pressure goal [53].

Recommended antihypertensive regimens

Nonpharmacologic therapy of hypertension. Restrict salt intake (Table 1, and later in this article). Lose excess weight. Avoid more than two drinks of alcohol per day as well as vasoconstrictor nose drops or eye drops, decongestants, amphetamines, anabolic steroids, high-dose estrogen therapy, cocaine, amphetamines, and yohimbine [7].

Initial pharmacologic therapy of hypertension. The sequence shown here is that recommended until the patient reaches his or her blood pressure goal: (*1*) low-dose ACE I therapy (starting dose recommended by manufacturer) plus dietary salt restriction (Table 1); (*2*) moderate-dose ACE I therapy (2 to 4 times the recommended starting dose) plus dietary salt restriction; or (*3*) moderate-dose ACE I therapy plus dietary salt restriction plus diuretic therapy. Furosemide is the recommended diuretic because it is more effective than thiazide diuretics in impaired kidney function and is less expensive than the other loop diuretics, bumetanide, and torsemide. In ADPKD patients, diuretic therapy may promote cyst growth [54] and is associated with more rapid progression, compared with ACE I therapy (abstract; Ecder et al, *Am Soc of Nephrol* 10:415, 1999). Thus, avoid diuretic therapy and emphasize NaCl restriction in ADPKD patients.

If the blood pressure goal is not being met with this regimen, we recommend that the patient's blood pressure-measuring technique and equipment should be checked again for accuracy, and their drug and dietary compliance be assessed. To estimate dietary salt intake accurately, 24-hour urine creatinine and sodium excretion should be measured. If the patient is receiving $NaHCO_3$ therapy, 24-hour urine chloride should be measured. Note that unless advanced renal insufficiency is present, $NaHCO_3$ therapy does not usually lead to sodium retention [55].

If the patient is compliant with the measures described previously in this article and blood pressure still is not at goal, we recommend using triple antihypertensive therapy, rather than increasing ACE I and diuretic therapy to high levels (discussed later in this article; see *ACE I therapy*).

Triple antihypertensive therapy. The sequence listed is the approximate level of recommendation.

ACE I, diuretic, and nondihydropyridine calcium channel blocker (ND-CCB, diltiazem and verapamil). The ND-CCBs in current clinical use are diltiazem and verapamil. The sustained release preparations are recommended starting at 120 to 180 mg daily. Diltiazem has fewer side effects, but is considerably more expensive. The combination of an ACE inhibitor and a ND-CCB is more antiproteinuric at the same blood pressure level than either drug taken alone [56–58]. The dihydropyridine CCBs (D-CCB; for example, nifedipine, amlodipine, felodipine, nicardipine) are not recommended in patients with renal disease, unless the D-CCBs are required to achieve blood pressure control. The concern is that the D-CCBs are not antiproteinuric and may actually worsen proteinuria, unless strict blood pressure control is achieved (for example, systolic blood pressure $\leq$110 mm Hg) [59]. If blood pressure control is not achieved with D-CCB, proteinuria may worsen, and faster progression of renal disease may occur [12].

ACE I, diuretic, clonidine. This combination is recommended for individuals receiving insulin (clonidine does not importantly affect glucoregulation) and for those who may have difficulty with β-blocker therapy (bronchospasm, cardiac conduction). Clonidine tablets are inexpensive but must be taken at least twice daily. The clonidine patch is convenient but more expensive.

ACE I, diuretic, β-blocker. This combination is appropriate for patients with coronary artery disease. β-Blockers can slow recovery from insulin-induced hypoglycemia but are not contraindicated in diabetes if needed for blood pressure control. In patients prone to diabetes, β-blocker therapy appears to increase (by 28%) the risk of developing diabetes [60]. This should be taken into account when selecting antihypertensive therapies.

ACE I, diuretic, α-1 blocker. This combination is generally well tolerated and effective. The α-1 blockers ameliorate the symptoms of prostatism. The ALLHAT study recently discontinued the arm that compared the α-1 blocker doxazocin 1 to 8 mg daily to chlorthalidone 25 mg daily as monotherapy to control hypertension. They found a 25% greater incidence of hospitalization for congestive heart failure in those randomized to doxazocin (National Institutes of Health Web site). However, the African American Study of Kidney Disease and Hypertension (AASK) External Monitoring Committee determined to continue to use doxazosin in combination therapy. The congestive heart failure seen in the doxazosin-treated ALLHAT patients may have been the result of inadequate diuretic therapy.

If triple therapy does not achieve the blood pressure goal, the patient should be re-evaluated for drug and dietary compliance. If that evaluation is negative, the patient should be studied by ambulatory blood pressure monitoring (ABPM) to determine whether sustained hypertension is present [61]. If sustained hypertension is documented by ABPM, secondary causes of hypertension should be sought, particularly renal artery stenosis.

If the evaluation for secondary causes of hypertension is negative, more intensive triple therapy is recommended. The initial step is usually an increase in diuretic therapy. A further increase in ACE I therapy is not recommended to achieve the blood pressure goal. Rather, high-dose ACE I therapy should be reserved for those who have achieved their blood pressure goal and dietary goals (for salt and protein) but have not achieved their proteinuria goal (discussed later in this article).

If more intense triple therapy does not achieve the blood pressure goal, quadruple antihypertensive therapy is recommended.

Quadruple antihypertensive therapy. The sequence listed is the approximate level of recommendation.

ACE I, diuretic, β-blocker, and dihydropyridine calcium channel blocker (D-CCB). This combination is usually highly effective in controlling blood pressure. The D-CCBs are more effective antihypertensive agents than the ND-CCBs, but may blunt the renal protection provided by ACE I therapy [56]. Thus, D-CCBs are recommended only if essential to achieving the blood pressure goal.

ACE I, diuretic, β-blocker, and minoxidil. Minoxidil may be unacceptable in women because it causes generalized hair growth. Minoxidil may worsen proteinuria, similar to D-CCB. Thus, minoxidil is recommended only if needed to achieve the blood pressure goal.

ACE I, diuretic, β-blocker, and α-1 blocker. The addition of a D-CCB or minoxidil will increase the effectiveness of this combination.

ACE I, diuretic, β-blocker, and clonidine. The combination of a β-blocker and clonidine can induce bradycardia but usually is well tolerated. The addition of a D-CCB or minoxidil will increase the effectiveness of this combination.

If the blood pressure goal is not achieved with quadruple therapy, we recommend that the issues of compliance and secondary hypertension be revisited.

2. ACE I therapy (Level 1)

There is now compelling evidence based on prospective, randomized, and controlled clinical trials that ACE I is renoprotective, independent of its antihypertensive effects, in both diabetic and nondiabetic nephropathies [1].

In diabetic nephropathy, ACE I renoprotection is seen

in both the early nephropathy (microalbuminuria) of both type 1 and type 2 diabetes and in the overt nephropathy of type 1 diabetes [1]. Evidence for renoprotection by ACE I in overt nephropathy of type 2 diabetes is less clear [1]. However, ACE I is believed to be renoprotective in these patients. Indeed, we have observed numerous instances of reversal of nephrotic syndrome and stabilization of renal function in type 2 diabetes during ACE I therapy (unpublished observations).

Evidence for ACE I renoprotection, independent of blood pressure control, has been shown only for overt nephropathy of type 1 diabetes [1]. Nevertheless, it is believed that ACE I is renoprotective independent of blood pressure control in other forms of diabetic nephropathy [62, 63].

The success of ACE I in forestalling the onset of overt proteinuria in diabetic patients with microalbuminuria has given rise to the question of whether ACE I should be given to diabetics without nephropathy. This seems to be a prudent strategy given the results of the Heart Outcomes Prevention Evaluation (HOPE) trial showing that there are broad health benefits from chronic ACE I therapy and no identifiable health risks [64].

In nondiabetic nephropathy, ACE I has been shown to be renoprotective, independent of its effect to control blood pressure, but only in patients with nephrotic-range proteinuria [4]. Nevertheless, adjusting for the effects of blood pressure control on GFR decline provides evidence that ACE I is also renoprotective independent of blood pressure control in nephropathies with lesser levels of proteinuria (1 to 3 g) [65, 66].

The renoprotection provided by ACE I can be enduring. In diabetic nephropathy [67, 68] and nondiabetic nephropathy [69], follow-ups of 5 to 10 years show sustained remission of nephrotic syndrome and stable or even improving renal function in many patients [68, 69].

Renoprotection in humans has been documented using four different ACE I (enalapril, captopril, benazepril, and ramipril), and renoprotection is generally regarded as a class-specific effect of ACE I [70]. However, there are pharmacologic differences among ACE inhibitors that could be biologically significant [5, 71].

The controlled trials show that the amount of ACE I therapy needed to achieve renoprotection is modest (for example, ~3.0 mg ramipril daily, 5 mg enalapril daily, 10 mg benazepril daily, or 25 mg captopril 3 times daily). Whether larger doses of ACE I confer additional renoprotection is unknown [5].

Goal of ACE I therapy. ACE I therapy is used primarily to provide renoprotection. Evidence that renoprotection is being provided by the ACE I therapy is shown by improved blood pressure control and particularly by decreased proteinuria [4, 66]. However, ACE I drugs are not particularly potent antihypertensive agents in patients with chronic renal insufficiency. For example, in the Ramipril Efficacy in Nephropathy (REIN) trial, there was no difference in blood pressure control between the ramipril group and the placebo group [4]. Furthermore, in the meta-analysis of the randomized trials of ACE I therapy in nondiabetic renal disease, the mean difference in systolic blood pressure between the ACE inhibitor groups and the control groups was only −4 mm Hg [3]. Thus, the renoprotection provided by ACE I probably relates mainly to its effects to reduce proteinuria and to attenuate other actions of angiotensin II, as discussed previously in this article.

Because ACE I has only a modest effect to control hypertension, it should not be used as the principal agent to achieve the blood pressure goal. That is, if the blood pressure goal is not achieved with moderate dose ACE I and diuretic therapy, we recommend triple antihypertensive therapy, as discussed previously in this article. ACE I should be used to achieve the proteinuria goal (24-hour urine protein <1 g). The rationale for the proteinuria goal is that in the MDRD Study, the non-ADPKD patients with proteinuria <1 g/24 hours had the slowest rates of GFR decline [2]. Furthermore, the long-term follow-up of diabetic and nondiabetic nephropathy patients indicates that those who achieve the proteinuria goal generally have relatively stable renal function [68, 69].

Presently, it is not clear whether increasing the ACE I dose to high levels (for example, 4 to 8 times the recommended starting dose) increases its antiproteinuric effects and/or the degree of renoprotection. However, this would be a reasonable course of action in patients whose nephrotic-range proteinuria persists despite achieving their blood pressure and dietary goals, while receiving at least moderate dose ACE I therapy. Of note, increasing the lisinopril dose from 8 to 20 mg daily does not increase its antiproteinuric effect [72]; however, high-dose ACE I therapy may have benefits. The trials of ACE I therapy in congestive heart failure suggest that high-dose ACE I therapy is better than low-dose therapy in prolonging patient survival [73]. Also, the high-dose ACE I therapy was generally well tolerated.

Determinants of the antiproteinuric response to ACE inhibitors. The ACE genotype may influence progression of renal disease [74] and the effect of ACE inhibition to decrease proteinuria and slow progression of renal disease [75]. The latter has been suggested by a recent re-evaluation of the REIN study in light of the patients' ACE gene polymorphism. ACE I therapy in those homozygous for the deletion (D) polymorphism showed greater reductions in proteinuria and greater slowing of GFR decline than those homozygous or heterozygous for the insertion (I) polymorphism [75]. However, in diabetics with mild renal manifestations, the opposite association of ACE I therapy with ACE gene polymorphism was found [76].

With respect to the renal mode of action of ACE I or

angiotensin receptor blockers (ARBs), it has been shown that plasma renin levels do not predict the renal hemodynamic response to either ACE I or ARB therapy. This suggests that intrarenal production of angiotensin II, rather than circulating angiotensin II, is the more important factor in determining the renoprotective effects of ACE I or ARB therapy [77].

ACE I therapy in those with impaired renal function. ACE I therapy is renoprotective even in those with substantially impaired kidney function (serum creatinine ≥2.5 mg/dL) [4, 66, 68, 78, 79]. Thus, impaired kidney function is not a contraindication to ACE I therapy; however, greater caution is advised.

If hyperkalemia develops on ACE I therapy, it is important to determine whether the hyperkalemia occurred despite a restricted K^+ intake. A 24-hour urine for creatinine and potassium best assesses this question. Our experience suggests that if the 24-hour urine for K^+ exceeds 50 mEq/24 hours, a reduction in potassium intake should prevent serious hyperkalemia. However, if the hyperkalemia occurred when a 24-hour urine for K^+ was less than 40 mEq/24 hours, it is unlikely that hyperkalemia can be avoided by dietary measures alone. In that circumstance, an increase in diuretic therapy (if the blood pressure is above goal) or sodium bicarbonate therapy (if plasma bicarbonate is less than normal) may control the hyperkalemia. If the hyperkalemia persists despite these measures, it is best to stop the ACE I. ARB therapy should then be considered because of its lesser tendency to raise serum K^+ (discussed later in this article).

Usually serum creatinine increases slightly with ACE I therapy (for example, increases of 0.2 mg/dL for patients with serum creatinine near 2 mg/dL) [66]. If it is a stable increase in serum creatinine, there is no need to discontinue the ACE I therapy.

Interaction of ACE I therapy with other interventions that reduce proteinuria. The addition of ACE I therapy to a low protein diet appears to increase the effect of these therapies to reduce proteinuria further [80] and slow GFR decline [81]. Thus, the combination of ACE I therapy and dietary protein restriction can be recommended.

The addition of indomethacin to ACE I therapy or ARB therapy also enhances their antiproteinuric effects [82]. However, we do not recommend chronic NSAID therapy to reduced proteinuria because of its nephrotoxicity (discussed both previously and later in this article). Also, our experience using NSAIDs with ACE I as an antiproteinuric therapy has generally been disappointing in those with severe proteinuria—the patients who would benefit most from a reduction in proteinuria. In those with minor proteinuria, the benefit of a small further reduction in proteinuria by the addition of indomethacin to ACE I or ARB therapy [82] might be offset by NSAID nephrotoxicity.

ARB therapy. These drugs are antiproteinuric and antihypertensive in a fashion similar to that of ACE I [83]. ARBs have a favorable side effects profile in that, compared with ACE I, ARBs are less likely to cause cough, angiedema, or hyperkalemia [83]. ARBs are renoprotective in experimental nephropathy [70] and suppress fibrogenic and inflammatory mechanisms similar to ACE I [84]. Whether ARBs are renoprotective in humans is unknown. However, there are two ongoing controlled clinical trials in type 2 diabetes that will assess renoprotection by losartan and irbesartan, respectively.

In patients who are intolerant of ACE I (hyperkalemia, cough, angiedema, hypersensitivity), ARB therapy is recommended. There is no information to guide therapy for renoprotective effects of the ARBs; however, the same general guidelines recommended for ACE I therapy may be appropriate for ARB therapy (discussed previously in this article).

Combination of ACE inhibitor and ARB therapy. Combining these agents has theoretical advantages because ACE I therapy alone or ARB therapy alone has therapeutic loopholes. For ACE I therapy, one loophole is that a substantial portion of the angiotensin II generated is formed by chymase, which is not inhibited by ACE I therapy [85]. ARB therapy does not suffer from this loophole because ARBs directly block the angiotensin II type 1 (AT1) receptor. On the other hand, ARBs do not inhibit the degradation of bradykinin (as do ACE Is) and bradykinin may have an important antihypertensive effect [85]. Also, ARBs do not significantly suppress aldosterone production, whereas ACE I drugs do suppress it [72] (abstract; Bakris, *J Am Soc Nephrol* 10:68A, 1999). If aldosterone induces tissue fibrosis [24], therapies such as ACE I that suppress aldosterone would have a therapeutic advantage. Combined ACE I and ARB therapy may make ARB therapy more efficient because less Ang II formation (by ACE I) allows the ARB to compete better for the AT1 receptor [85].

In a small study involving IgA nephritis patients, the combination ACE I/ARB therapy was more effective in reducing proteinuria than either therapy alone, despite similar blood pressure levels [86]. Several clinical trials are currently evaluating combination ACE I/ARB therapy in heart disease and in renal disease, respectively.

3. Control blood glucose in diabetics (Level 1)

For type 1 diabetics, the Hgb A1C goal should be within two percentage points of the upper limits of normal for the particular Hgb A1C assay [87, 88].

For type 2 diabetics, the goal is a normal Hgb A1C. This recommendation is based on the two major intervention trials in type 2 diabetes, one involving insulin therapy [89], the other involving oral hypoglycemic agents and insulin [90]. In each of these studies, normalization of the Hgb A1C was achieved for prolonged periods

in many of the study patients. In type 2 diabetes, oral hypoglycemic agents that control blood glucose at lower blood insulin levels such as metformin, rosiglitazone, or acarbose have theoretical advantages over sulfonylureas, which control blood glucose but increase endogenous insulin levels [91]. High endogenous insulin levels are a strong risk factor for adverse cardiovascular outcomes. Thus, measures that control blood glucose at lower insulin levels may reduce cardiovascular risk. This may also slow the development of glomerulosclerosis (discussed later in this article). Of interest is the recent report that the thiazolidinedione compounds (for example, Avandia, Actos) are renoprotective, independent of their insulin-sensitivity effects [92].

4. Dietary measures

Protein intake (Level 1). Based on the meta-analyses and secondary analyses of the randomized trials, it can be concluded that protein restriction slows progression of renal disease by about 0.5 mL/min/year) [2, 93–95].

When patients are instructed in a dietary protein intake of 0.6 g/kg ideal body weight/day, the average achieved dietary protein intake is 0.7 to 0.8 kg/ideal body weight/day. This and lower levels of dietary protein intake are associated with slowed renal disease progression [95].

There are no known risks to a low protein diet. However, in patients with heavy proteinuria, we recommend that for each gram of proteinuria exceeding 3 g/24 hours, protein intake be increased by 1 g daily [2, 96]. There are no known health benefits to a higher protein diet. Indeed, a higher protein diet, particularly meat proteins, can raise blood pressure, increase pathogenic blood lipids, and promote hypercalciuria in those with normal GFR [7]. Thus, recommending the low protein diet appears to be a "no-lose" proposition [97].

Our experience is that most patients are able to maintain a low protein diet apparently without great effort and without ongoing dietary counseling. We periodically monitor dietary protein intake by measuring the creatinine and urea content in a 24-hour urine collection.

The benefit of the low protein diet in the MDRD Study occurred in those with GFRs between 12.5 and 55 mL/min/1.73 m^2. Whether it is beneficial to introduce the low protein diet at higher levels of GFR is unknown. However, given the diet's safety and probable efficacy, the low protein diet can be recommended even in early progressive renal disease.

Another reason to recommend the low protein diet in progressive renal disease, even in those with little or no loss of GFR, is that the low protein goal slows the increase in proteinuria over time [98]. The effect is almost identical to that of the low blood pressure goal, as shown in Figure 3. Thus, the low protein goal slows the progression from minor proteinuria to major proteinuria, which is a strong risk factor for renal disease progression [50].

In diabetic nephropathy, the GFR decline is also slowed by the low protein diet. Indeed, this effect is greater in diabetic than nondiabetic nephropathy [94]. Also, the low protein diet may delay the onset of microalbuminuria and slow its progression in type I diabetes [99].

Salt (NaCl) intake (Level 2). The NaCl goal of 80 to 120 mmol/day is arbitrary as a renoprotective measure. Its rationale is based on JNC-6 recommendations for control of blood pressure [61] and the studies showing that a high salt diet can completely override the effect of ACE I or ND-CCB to reduce proteinuria [32, 33]. A diet containing 80 to 120 mmol NaCl daily can be made more palatable if no salt is used in food preparation but a small amount of salt is added to the surface of the food as it is eaten [55]. For example, a 2 g sodium diet (88 mmol NaCl) is prescribed. In addition, the patient is allotted 20 to 40 mmol NaCl each day as surface salt. This can be given as ⅓ teaspoon of NaCl in a salt shaker (approximately 25 mmol of NaCl) or as one or two four-chamber salt packets (1 g, 17 mmol/L NaCl per packet), the type commonly available in fast food restaurants.

Diuretic therapy can be used to restore the antiproteinuric effects of ACE I when the patient is not compliant with a low salt intake [100]. However, the combination of high salt intake and diuretic therapy can lead to significant hypokalemia [55], which itself may promote progression of renal disease (discussed previously and later in this article). Dietary salt intake should be monitored by a periodic measurement of 24-hour urine creatinine and sodium, as discussed previously in this article.

Fluid intake (Level 2). Analysis of the MDRD study showed a significant association between high fluid intake (high mean follow-up 24-hour urine volume and low mean follow-up U_{Osm}) and more rapid progression of renal disease (abstract; Hebert et al, *J Am Soc Nephrol* 11:148A, 2000). The magnitude of the association is relatively large: The difference in GFR decline, adjusted for covariate of renal disease progression, is 1.0 to 1.5 mL/min/year greater in those in the highest quartile of 24-hour urine volume (>2.85 L) compared with those in the lowest quartile of 24-hour urine volume (<2.0 L). Thus, based on this secondary analysis of the MDRD Study A patients (GFR 25 to 55 mL/min/1.73 m^2, median serum creatinine 1.9 mg/dL), we suggest that in contrast to some current opinions, chronic high fluid intakes should not be generally recommended in patients with chronic renal insufficiency. This advice may be particularly important in ADPKD patients.

5. Control blood lipids (Level 1 for general benefit, Level 2 for renal benefit)

Abundant literature suggests that controlling blood lipids may slow progression of diabetic and nondiabetic

renal disease. The randomized clinical trials have been disappointing since only small numbers of patients have been studied [reviewed in 101]. Nevertheless, the MDRD Study showed that low high-density lipoprotein cholesterol was an independent risk factor for progression of renal disease [31], and there is similar evidence that high cholesterol and perhaps high triglyceride levels promote progression of diabetic glomerulosclerosis [reviewed in 102]. In the ARIC study (cited previously in this article in relationship to procoagulants), low high-density lipoprotein cholesterol and high triglycerides were independent risk factors for a significant increase in serum creatinine during follow-up. There is conclusive evidence that controlling blood lipids protects against atherosclerosis [103]. Thus, it is advisable to encourage blood lipid control in patients with progressive renal disease.

The suggested goals for blood lipid control are arbitrary. However, given the recent evidence that reducing low-density lipoprotein cholesterol with statin drugs to $<$100 mg/dL (mean 70 mg/dL) is well tolerated and associated with control of angina [104] suggests that a similar goal might be appropriate in patients at risk for progressive renal disease.

Of note, 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors have anti-inflammatory effects by blocking NF-κB activation, a transcription factor for inflammatory pathways, including the chemokine MCP-1 [reviewed in 105], which is expressed in both inflammatory and noninflammatory renal diseases [25]. Thus, inflammatory glomerulopathies might be benefited particularly by this therapy.

6. No cigarette smoking (Level 1 for general benefit, Level 2 for renal benefit)

Cigarettes are bad for everything, even the kidneys (discussed previously in this article).

7. Avoid NSAID agents (Level 2)

In patients with impaired kidney function and chronic pain, we prescribe analgesic medications that are not known to have nephrotoxicity: plain aspirin, prolonged-release aspirin, acetaminophen, propoxyphene, or tramadol. Note that the combinations of acetaminophen and aspirin or acetaminophen and an NSAID may be nephrotoxic [reviewed in 106].

8. Control homocysteine level (Level 2 for cardiovascular benefit, Level 3 for renal benefit)

The goal is to normalize plasma homocysteine. However, this is difficult in patients with advanced renal insufficiency in whom only partial reductions in homocysteine levels are seen despite high-dose folic acid therapy and supplementation with vitamins B_6 and B_{12} [107]. Recent evidence suggests that intravenous therapy with folinic acid may restore elevated homocysteine levels to normal in chronic hemodialysis patients [107]. However, such therapy is not practical in nonhemodialysis patients.

Vitamin B_{12} levels must be normal when dosing with folic acid so that vitamin B_{12} depletion of the central nervous system does not occur. Severe vitamin B_{12} deficiency can result in dementia or subacute combined degeneration. We commonly use folic acid doses of 5 to 10 mg daily.

9. Control hyperinsulinemia (Level 3)

Weight reduction in obese patients and exercise decrease insulin resistance in patients with elevated C-peptide levels. Thus, these therapies can be recommended as a general health measure. In addition, hyperinsulinemia may promote progression of glomerular sclerosis, as discussed previously in this article. Whether more aggressive measures to reduce insulin resistance, such as therapy with rosiglitazone, or metformin, should be recommended in patients with high C-peptide levels, and evidence of progressive glomerulopathy is not clear. However, these agents are generally well tolerated and do not provoke hypoglycemia.

10. Correct anemia (Level 2)

In a randomized trial that demonstrated slower progression of renal disease with correction of anemia by erythropoietin therapy, the achieved hematocrit was 32% in the erythropoietin group and 25% in the control group [45]. Thus, the goal hemoglobin of 11 to 12 g/dL seems appropriate. This is also the hemoglobin goal for renal failure patients in the National Kidney Foundation Dialysis Outcomes Quality Index (DOQI) guidelines. The renoprotective effect of anemia correction is greater in nondiabetics than diabetics and may require initiation of erythropoietin therapy before the serum creatinine exceeds 4.0 mg/dL [45].

11. Use antioxidants (Level 3)

Oxidant stress may induce tissue injury and play a role in progression of renal disease. Participants include plasma homocysteine, plasma lipoproteins, ferric iron, and vitamin E deficiency (discussed previously in this article). Based on an animal model of diabetic nephropathy, a dose of 200 mg of vitamin C has been recommended in humans [108]. High-dose vitamin C therapy is not recommended because it might lead to excessive deposition of calcium oxalate in tissues. Vitamin E also mitigates oxygen stress and may be beneficial [109].

12. Avoid hypokalemia (Level 1 for general benefit, Level 3 for renal benefit)

In experimental models of renal disease, hypokalemia induces renal hypertrophy and interstitial fibrosis. In patients with chronic severe hypokalemia, progressive renal failure caused by tubular interstitial disease has been

well documented [47]. Chronic hypokalemia may also promote cyst growth in normal kidneys and ADPKD [54].

13. Control hyperphosphatemia (Level 1 for general benefit, Level 3 for renal benefit)

Dietary phosphorus restriction (~800 mg of elemental phosphorus daily) and phosphate binders are recommended to maintain the serum phosphorus level within the normal range. This may slow progression of renal disease (discussed previously in this article).

14. Low-dose aspirin therapy (Level 1 for general benefit, Level 3 for renal benefit)

Low-dose aspirin therapy is useful in the primary and secondary prevention of myocardial infarction and stroke in males [110], but the benefit is less clear in females. Aspirin therapy may also attenuate the effects of increased procoagulants that may promote progression of renal disease (discussed previously in this article). Aspirin 81 mg daily ("baby" aspirin or one fourth of an adult aspirin) is recommended because it is well tolerated and has a more selective effect on the coagulation system compared with higher dose aspirin therapy [111].

Aspirin therapy may not be appropriate in ADPKD (may promote cyst hemorrhage) or in those at increased risk of a hemorrhagic stroke (poorly controlled hypertension, Asians, very low serum cholesterol, or family history of intracerebral hemorrhage) [110]. In the older population, low-dose aspirin therapy has been reported to cause a small (5 to 10%) increase in serum creatinine, uric acid, and blood urea nitrogen level [112]. Aspirin therapy does not attenuate the cardiovascular benefits of ACE I therapy as was once thought [113]. Combination dipyridamole-aspirin therapy may be even more effective than aspirin therapy alone, as it is in stroke prevention [114].

15. Estrogen replacement therapy (Level 2 for general benefit, Level 3 for renal benefit)

There are multiple theoretical reasons why estrogen and androgen effects may explain the slower progression of renal disease in women than men. However, estrogen therapy may promote sodium retention, worsen hypertension, and increase production of pathogenic plasma lipids [115]. These should be corrected if estrogen replacement therapy is used. In men with renal disease, it may be prudent to avoid androgen therapy.

RENAL CONDITIONS FOR WHICH RENOPROTECTIVE THERAPY IS USUALLY INDICATED

Any patient with a chronic nephropathy (diabetic, nondiabetic, or polycystic) who is at risk for progression is a candidate for the multiple risk factor intervention strategy. We recommend that therapy be started early and even preemptively because the renoprotective interventions may be more effective if used before overt proteinuria or GFR reduction is present. During pregnancy therapies such as ACE I, ARBs, HMG-CoA reductase inhibitors, or low-protein diet should be discontinued.

ADPKD requires special mention because ACE I therapy did not slow ADPKD progression in the AIPRI trial [66], and blood pressure control and low-protein diet did not influence ADPKD progression in the MDRD Study [2]. Despite these negative outcomes, ACE I therapy, strict blood pressure control, and low-protein diet are recommended in ADPKD because studies in the genetic models of PKD show benefit in preventing cyst growth if these interventions are begun early [116]. Furthermore, ACE I therapy has general benefits, which include cardiovascular benefits [64]. In experimental models of PKD, HMG CoA reductase inhibitor slows renal cyst growth [116]. Thus, this class of drugs may also be useful in human ADPKD. Finally, it may be important to avoid a high fluid intake and diuretics in ADPKD patients, as discussed previously in this article.

Patients with directly treatable forms of nephropathy such as idiopathic membranous nephropathy or lupus nephritis should also be managed with the multiple risk factor intervention strategy because the proteinuria is nonselective and often is chronic. Thus, measures that reduce proteinuria may be adjunctive to the immunosuppression therapy to induce remission of the nephropathy [42].

Those with congenital solitary kidney or solitary kidney that was acquired in childhood should be considered for renoprotective therapy. These patients appear to be at increased risk to develop progressive proteinuria and decline in kidney function [117]. Note that in 27 of the MDRD Study patients, the only renal diagnosis was solitary kidney [50].

RENAL CONDITIONS FOR WHICH RENOPROTECTIVE THERAPIES USUALLY ARE NOT INDICATED

Some patients with nephropathy are at little or no increased risk for progressive renal disease. In these patients, renoprotective strategies are not generally recommended. These include the following:

Steroid-responsive minimal change disease (MCD). However, if proteinuria should become persistent and steroid resistant, the renoprotective strategies are recommended.

A solitary kidney that is normal and acquired in adulthood, for example, kidney donor. Although kidney donors apparently are not at increased risk for progressive renal insufficiency [42], periodic monitoring for hyper-

tension and abnormal proteinuria or serum creatinine levels is recommended.

Hereditary nephritis in the adult whose only renal manifestation is microscopic hematuria and who is normotensive. Our experience suggests that this condition does not progress. Nevertheless, periodic monitoring is recommended.

Thin glomerular basement membrane (GBM) disease in the adult whose only renal manifestation is microscopic hematuria and who is normotensive. Only rarely do these patients develop proteinuria and impaired kidney function [118]. Thus, renoprotective interventions are not recommended but periodic monitoring is appropriate.

Elderly patients with idiopathic and moderately elevated serum creatinine levels (1.4 to 2.0 mg/dL) and minor proteinuria (<1 g/24 hours) whose renal parameters have been stable for at least one year. These patients usually die of nonrenal causes. Thus, renoprotective strategies probably are more of a nuisance than a benefit in these patients.

Renal conditions that cause acute renal failure but complete or nearly complete recovery of kidney function can be expected. These conditions include acute postinfectious glomerulonephritis (GN), the GN of chronic infection (for example, endocarditis), obstructive uropathy, acute tubular necrosis from toxins, or ischemia. If the serum creatinine level does not return to normal or if abnormal proteinuria persists, the multiple-risk-factor intervention strategies are recommended.

PRACTICALITY OF A MULTIPLE-RISK-FACTOR INTERVENTION TO SLOW PROGRESSION OF RENAL DISEASE

Our experience suggests that we achieve most of the Level 1 and Level 2 interventions in the majority of patients with chronic nephropathies. One strategy that appears to help our patients achieve compliance is a monograph that we prepared for their physicians, but it is written so that the information is also accessible to the average patient. We suggest that the current Perspectives in Renal Medicine could also serve this purpose, especially Table 1.

ESTIMATING THE BENEFITS OF THE MULTIPLE-RISK-FACTOR INTERVENTION

The magnitude of the benefit of multiple-risk-factor intervention is speculative. However, there are certain benchmarks that can be used. For example, in the MDRD Study, achieving the blood pressure and dietary goals slowed progression of renal disease by an average of approximately 1 mL/min/year [2, 119]. Furthermore, a secondary analysis of the MDRD Study showed that for each 1 g reduction in proteinuria observed at four months of the blood pressure and diet intervention, subsequent GFR decline was slowed by about 1 mL/min/year [50]. The MDRD Study also suggests that avoidance of excessive fluid intake could slow progression of renal disease by as much as 1 to 1.5 mL/min/year, as discussed previously in this article. The other recommended measures to slow progression of renal disease (Table 1) may add further to renoprotection. Indeed, there are no a priori grounds to suggest that the recommended renoprotective therapies are antagonistic to one another.

Although it is likely that the multiple-risk-factor intervention is beneficial, it would be highly desirable to know how much benefit is achieved. To do that would require a prospective trial in which patients are randomized to usual care or to the multiple-risk-factor intervention. As we have previously suggested, such a study would be more informative and efficient than a series of clinical trials in which the mechanisms of progression are studied singly or only a few at a time [6].

If such a study were undertaken, it would be similar to the MR FIT study [120]. It seems unlikely, however, that such a study will be undertaken in the near future. In the meanwhile, nephrologists must make prudent decisions regarding our patients using evidence that may not be conclusive. We suggest that the multiple-risk-factor intervention that is proposed in this article is a plausible and prudent approach to the formidable problem of progression of renal diseases for which no specific therapy is available.

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APPENDIX

Abbreviations used in this article are: AASK, African American Study of Kidney Disease and Hypertension (study); ABPM, ambulatory blood pressure monitoring; ACE, angiotensin-converting enzyme; ACE I, angiotensin-converting enzyme inhibitor; ADPKD, autosomal polycystic kidney disease; AIPRI, Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency (study); Ang II, angiotensin II; ARB, angiotensin receptor blocker; ARIC, Atherosclerosis Risk in Community (study); AT1, angiotensin II type 1 (receptor); BUN, blood urea nitrogen; D-CCB, dihydropyridine calcium channel blocker; DOQI, the National Kidney Foundation Dialysis Outcomes Quality Index (study); ET-1, endothelin-1; FSG, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; GFR, glomerular filtration rate; GN, glomerulonephritis; HDL, high density lipoprotein; HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A; HOPE, Heart Outcomes Prevention Evaluation (study); IGF-1, insulin-like growth factor-1; LDL, low density lipoprotein; MAC, membrane attack complex; MCD, minimal change disease; MDRD, Modification of Diet in Renal Disease (study); ND-CCB, non-dihydropyridine calcium channel blocker; NSAIDs, nonsteroidal anti-inflammatory agents; PDGF,

platelet-derived growth factor; PKD, polycystic kidney disease; REIN, Rampiril Efficacy in Nephrology (study); TGF-β, transforming growth factor-β.

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